REMARKS

This Amendment is submitted in full response to the Office Action dated April 21, 2006. A request for an extension of time and a check for the appropriate fees associated therewith are being filed concurrently herewith. Thus, in consideration of the remarks and amendments presented herein, Applicant respectfully requests reconsideration of this application.

To begin, Applicant acknowledges election of the invention of Group III, and that original claims 60-65 and newly presented claims 67-70 read on the elected invention. Further, claims 1-59 and 66 are hereby withdrawn, without traverse, however, Applicant reserves the right to represent any or all of the withdrawn claims upon allowance of a generic claim or in a continuing application.

Looking to the present Office Action, claims 60-65 stand rejected under 35 U.S.C. §103(a) as being unpatentable over various references cited in the Office Action. Additionally, the claims stand rejected under 35 U.S.C. §112, second paragraph.

Applicant is appreciative of the Examiner's detailed and conscientious review of this application, and respectfully asks for conscientious reconsideration of same, in light of the amended and newly presented claims herein, and the following remarks.

As an initial matter, several claims have been amended in response to the rejections under 35 U.S.C. §112, and the specification has been amended to clarify heparin concentrations, and to correct typographical errors and omissions.

I. Rejection of Claims Under 35 U.S.C. §112.

To begin, and as noted above, Applicant has amended several claims in view of the rejections under 35 U.S.C. §112, second paragraph. Specifically, independent claim 60 has been amended to clearly recite that a "blood specimen solution" is a "blood specimen" extracted from the patient and added to an anti-coagulant, such as heparin, as disclosed in the specification at page 30, lines 3-8, as well as on pages 47 and 50.

In addition, the recitation of a "supernatant plasma-cell layer" in independent claim 60 has been amended to recite a "supernatant of blood plasma comprising white blood cells," as disclosed in the specification on page 30, lines 11 and 12, and on page 47, lines 23-24. The specification does not disclose or discuss an interface "buffy coat" cell layer in any manner, and as such, Applicant is uncertain why the Office Action suggests reading such a limitation into the original claim recitation. Further, "supernatant" as recited in the original claims and as would be understood by one of ordinary skill in the art at the time of the invention is a "liquid or fluid forming a layer on the surface of another liquid,"[1] not an underlying intermediate or interface layer, as is incorrectly suggested in the Office Action. However, in the interest of moving the present application to allowance, independent claim 60 has been amended to recite a "supernatant of blood plasma comprising white blood cells," thereby eliminating any

[1] Hawley's Condensed Chemical Dictionary, 11th Ed., Van Nostrand Reinhold, New York, 1987, pg. 1111.

possible confusion as to the scope of the claimed subject matter.

In view of the above, the recitation of a "plasma-cell solution" and a "plasma-cell fraction," which are derived directly and indirectly from the "supernatant of blood plasma comprising white blood cells," respectively, particularly point out and distinctly claim the subject matter of Applicant's present invention. With regard to the "plasma-cell solution," claims 60 and 63 have been amended to further clarify that the "plasma-cell solution" is formed by inducing a hypotonic shock in the "supernatant of blood plasma" via dilution.

Finally, the recitation of the step of "fractioning" has been replaced with the step of "heating." In view of the foregoing, claims 60-65, as amended herein, particularly point out and distinctly claim the subject matter of Applicant's present invention and, as such, the rejection of claims 60-65 under 35 U.S.C. §112 is overcome.

II. Rejection of Claims Under 35 U.S.C. §103.

Before addressing the substantive issues with regard to the rejection of the claims under 35 U.S.C. § 103, Applicant respectfully points out the well established requirement:

> For a prior art reference to anticipate in terms of 35 U.S.C. §102, every element of the claimed invention must be identically shown in a single reference. Diversitech Corp. v. Century Steps, Inc., 7 USPQ2d 1315, 1317 (Fed. Cir. 1988).

Moreover, this burden on the U.S. Patent and Trademark Office

("PTO") is further compounded by the fact that the Federal Circuit has stated that within the single reference:

> [t]he identical invention must be shown in as complete detail as is contained in the patent claim. Richardson v. Suzuki Motor Co. Ltd., 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

And, more recently, the Federal Circuit has further expanded this principle to include that:

> An anticipating reference must describe the patented subject matter with sufficient clarity and detail to establish that the subject matter existed in the prior art and that such existence would be recognized by persons of ordinary skill in the field of the invention. Crown Operations Int'l, Ltd. v. Solutia Inc., 289 F.3d 1367, 62 USPQ2d 1917, 1921 (Fed. Cir. 2002).

As such, if an Applicant can establish that at least one claimed element is not present or is not identically disclosed in as complete detail in a prior art reference put forth by the PTO, the grounds for rejection pursuant to 35 U.S.C. §102 of each claim comprising that element have been overcome.

Furthermore, once the grounds for rejection under 35 U.S.C. §102 have been overcome, the PTO cannot merely turn to 35 U.S.C. §103 as a basis for maintaining a rejection without first meeting the requisite burden. Specifically, the decisions of the Federal Circuit instruct that:

> In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art [and further that] the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification. In re Fritch, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992).

More recently, this point was further emphasized by the Federal Circuit, which added that:

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the [Examiner] to show a motivation to combine the references that create the case of obviousness. In other words, the [Examiner] must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.
>
> This court has identified three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. Beckson Marine, Inc. v. NFM, Inc., 292 F.3d 718, 63 USPQ2d 1031, 1037 (Fed. Cir. 2002); citing In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

A. Rejection of Claims Under 35 U.S.C. §103 is Moot.

In view of the amendments to the claims as discussed above, the rejection of claims 60-65 under 35 U.S.C. §103 is rendered moot because the grounds for rejection stated in the Office Action are based on the incorrect assumption that the "supernatant," "plasma-cell layer," and "plasma-cell solution" comprise plasma and an interface cell layer (buffy coat), and that the "blood specimen solution" consists solely of a blood sample. In accordance with the foregoing discussion of the amended claims presented herein, these assumptions are clearly in error.

B. Failure to Establish *prima facie* Obviousness.

Regardless, Applicant wishes to address the rejection of the claims under 35 U.S.C. §103, as the cited references, even when

combined in total, fail to establish a *prima facie* case of obviousness. The Office Action states that:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make **an autologous hemoderivative composition *comprising plasma and interface cell lysate*** in view of the teachings of Lasalvia and Moingeon. (***emphasis added***)

Applicant respectfully disagrees with this conclusion, and asserts that even a combination of <u>all</u> of the references cited in the Office Action fails to render Applicant's invention, as claimed herein, obvious and unpatentable. To begin, and as the Examiner has correctly stated, the primary reference relied upon, Lasalvia, **"does not teach how to make the autologous blood fraction from cancer patients."** The Office Action, however, then incorrectly maintains that this deficiency is somehow made up for in the teachings of the numerous and varied references cited therein.

However, Applicant maintains that none of the cited references, either alone or in any combination, teach any autologous hemoderivative composition for use in eliciting an effective antitumoral immune response in a patient, much less, a method for the preparation of such a composition as recited in claims 60-65, either as originally filed or as amended herein.

To begin, the reference to Moingeon, is cited as teaching "various kinds of cancer vaccine[s]," however, in the litany of vaccines disclosed by Moingeon and listed in the Office Action,

none comprises an autologous hemoderivative composition. Further, Moingeon actually teaches away from autologous compositions, such as are disclosed and claimed in the present application. Specifically, Moingeon discusses the advantages of antigens specific to a single tumor beginning in the last paragraph on page 1311, but concludes stating:

> One limitation however is that multiple mutations can often be found in a given target antigen, implying a need for typing the tumor, in order to develop a customized cancer vaccine [which] ***renders this approach likely to preclude large scale application.*** (***emphasis added***)

More importantly, Applicant notes that nowhere in the extensive list of vaccines does Moingeon disclose any autologous hemoderivative composition, or hint at any method for the preparation of the same.

Looking to the other references cited in the Office Action, their relevance to the present invention is minimal, if at all. More in particular, a number of references appear to have been cited for purposes of demonstrating that basic, individual steps utilized in the present method are known. However, none of the cited references, alone or in combination, teach or suggest in any manner the sequence of specific and individual steps required so as to allow a person of ordinary skill in the art to arrive at Applicant's present invention.

Specifically, the Office Action states that Ryan teaches that "blood plasma and interface cells can be prepared from a blood sample by mixing the blood with an anticoagulant and separating

from the red blood cells using any of the conventional methods such as centrifugation or settling;" Freshney teaches "isolation of the plasma and interface cells of the blood using heparin and centrifugation;" and, Somani teaches "collecting blood samples for plasma electrolytes and inulin measurements from the femoral artery of a dog." It is appreciated that each of the foregoing are standard clinical techniques which in no manner suggest or teach Applicant's new, novel, and non-obvious combination of steps which comprise his method for the preparation of an autologous hemoderivative composition.

With regard to the references to Colaco, Moore, and Mejza, they appear to be cited to demonstrate that cell lysing may be accomplished via dilution and, in the case of Colaco and Mejza, with the additional steps of freezing and thawing. As before, however, the fact that certain, specific clinical techniques employed by Applicant may be disclosed, these references do not suggest or teach the innovative combination of steps developed by Applicant for the preparation of an autologous hemoderivative composition, as disclosed in the present application and recited in the currently pending claims.

Looking more in particular to the reference to Moore, which is cited for teaching "lysing [tumor] cells with equal volume of distilled water," Applicant respectfully submits that Moore is directed to a culture medium for *in vitro* cultivation of mammalian cells. Further, the reference to harvesting tumor cells lysed with

distilled water does not teach or suggest the innovative autologous hemoderivative composition of the present invention, rather, it teaches away from the presently claimed invention. The Examiner is directed to the specification of the present application beginning on page 10, line 15, wherein Applicant clearly acknowledges and addresses some of the numerous deficiencies in reliance upon tumor cells collected from the patient:

> The second difficulty encountered in active specific immunotherapy relates to the preparation of a vaccine having the patient's malignant tumor as its source. Here, both quantitative and qualitative limitations are present. To begin with, the number of inoculations and the amount of immunogen, or vaccine, in each inoculation as required by **this technique are limited by the availability of surgical tumor specimens**, and the typically weak antigens which are present at low cellular concentrations therein. In addition, and as noted above with respect to adoptive specific immunotherapy techniques, if tumor cells modify their antigenic profile due to their high rate of mutation, the immune effectors elicited by inoculation of the original vaccine may not recognize a target in the remaining mutated tumor cells. As a result, repeated inoculations of the original vaccine will not usually be effective unless current surgical tumor specimens are available in order to prepare vaccines containing the successively mutated antigens, however, such current surgical tumor specimens are hardly, if ever, available. (**emphasis added**)

As such, the reference to Moore, as well as any other reference related to vaccines based upon tumor samples obtained from the patient, is inapposite to and teaches away from Applicant's novel and non-obvious method for the preparation of an autologous hemoderivative composition.

Lastly, the Office Action cites the reference to Heldebrant as teaching "heat inactivation of infectious agents contained in

plasma and in protein fractions" separated therefrom, and for "filtering protein through a sterilized bacteria-retention membrane or cartridge filter." Applicant respectfully submits that Heldebrant suggests heat as a means to sterilize, i.e., inactivate, infectious agents including viral components which may be present in biological material such as a protein fraction separated from blood plasma.

The use of heat in accordance with the Applicant's present invention, however, is not for purposes of sterilization. Rather, heat is utilized in the present invention to release tumor associated antigens. First, heat is used to release chaperone protected complexes from the blood cells, and second, heat is presented to induce an immunogenic release of the tumor associated antigens from the chaperone complex. This is supported by the present specification beginning at page 28, line 21:

> The present invention further provides a method for producing such an external vaccine. In particular, at least some of the plurality of TAA released into the patient's blood as molecular chaperone protected complexes as a result of the internal vaccine are distributed in blood cells and blood plasma where they may become associated by external adhesion or by phagocytosis. When such a blood specimen is exposed to a hypotonic and hypothermic shock, essentially all of the plurality of TAA-chaperone complexes are released from the blood cells, into a supernatant. Afterwards, the supernatant may be exposed to thermal fractioning, such as by heating to approximately 100 degrees centigrade for approximately between 8 to 10 minutes. Under these conditions, the TAA-chaperone complexes are opened, and the plurality of TAA become free.

Thus, is highly unlikely that Heldebrant's suggestion of heat for sterilization would motivate a person of ordinary skill in the

art at the time of the invention to combine Heldebrant with any or all of the remaining references cited to arrive at Applicant's new and innovative method for the preparation of an autologous hemoderivative composition.

Thus, Applicant respectfully asserts that the references cited in the present Office Action fail to establish a prima facie case of obviousness, either alone or in combination, and as such, claims 60-65, as amended herein, are in condition for immediate allowance.

C. Evidence in Rebuttal of *prima facie* Obviousness.

Finally, even if the cited references were found to establish a prima facie case of obviousness, Applicant submits herewith evidence which rebuts this basis for rejection of the claim.

First, in accordance with 37 C.F.R. §1.132, enclosed herewith as Attachment I is the Declaration of Applicant, Dr. Eduardo M. Lasalvia-Prisco (hereinafter "the Lasalvia Declaration"). Aside from establishing Applicant's considerable experience and expertise in the art, the Lasalvia Declaration presents an independent review and analysis of the innovate method presented herein by way of the Commentary of Dr, Leisha A. Emens, herself, a person with considerable expertise in the art, as is clearly established in the Lasalvia Declaration.

Applicant respectfully submits that the invention disclosed in the present application, and as recited in the claims pending herein, has been found to be novel, unique, and intriguing by a

person of considerable, if not extraordinary, skill in the art, and that the invention "offers multiple advantages [relative to known techniques]," in accordance with paragraph 16 of the Declaration. Further, in accordance with paragraph 17 of the Lasalvia Declaration, Dr. Emens indicates that the novel and unique method of the present invention fulfills a long felt need in the art.

Also enclosed herewith, and also in accordance with 37 C.F.R. §1.132, is Attachment II, the Declaration of Dr. Emilio Garcia-Giralt (hereinafter "the Garcia-Giralt Declaration). As may be seen from the Garcia-Giralt Declaration, Dr. Garcia-Giralt is also a person of considerable skill in the art and has practiced the method of the present invention on a patient who failed to respond to conventional treatments. Remarkably, following treatment with the inventive method disclosed herein, the patient appears to be in complete and total remission, per paragraph 13 of the Garcia-Giralt Declaration. Furthermore, the Garcia-Giralt Declaration states that the complete and total remission of Patient X is "completely unexpected," and that the French National Committee of Medical Experts requested the medical dossier of Patient X for review as a result of the unexpected recovery.

Thus, Applicant respectfully submits that the method for the preparation of an autologous hemoderivative composition as recited in the present claims in not obvious, but is novel and unique, as evidenced by experts the art. Further, evidence presented herein establishes that not only is the method of the present invention

novel and non-obvious, but that it fulfills a long felt need in the art, and that unexpected results have already been achieved though its implementation. Therefore, Applicant submits that claims 60-65, as amended herein, are new and non-obvious, and as such, are in condition for immediate allowance.

III. New Claims.

Applicant submits herewith new claim 67-70. More in particular, new independent claim 67 comprises the subject matter of independent claim 60, as amended herein, and includes further limitations including extracting a blood specimen from a patient "wherein the blood specimen comprises a plurality of tumor associated antigens."

New independent claim 68 also comprises the subject matter of independent claim 60, as amended herein, and adds a number of further limitations, including, among others: "generating a plurality of tumor associated antigen-chaperone complexes in a plurality of malignant tumor cells in the patient"; "causing the release of at least some of the plurality of tumor associated antigen-chaperone complexes into the patient's bloodstream"; "extracting . . . a blood specimen . . . wherein the blood specimen comprises at least some of the plurality of tumor associated antigen-chaperone complexes released into the patient's bloodstream"; and, "inducing an immunogenic release of a plurality of tumor associated antigens from the plurality of tumor associated

antigen-chaperone complexes and forming a plasma-cell fraction."

In addition, Applicant submits that the additional limitations presented in new claims 67-70 are fully supported by the present specification, and that no new matter has been introduced.

Thus, Applicant has established that at least one element recited in each of new independent claims 67 and 68 is not present or is not identically disclosed in as complete detail by any of the references cited herein, or elsewhere, and, as such, Applicant respectfully submits that these claims are new and non-obvious, and are clearly in condition for immediate allowance, as are the claims dependent therefrom.

IV. Conclusion.

Accordingly, based on the foregoing Amendments and Remarks, the Examiner is respectfully requested to reconsider the present application. Specifically, Applicant maintains that independent claims 60-65, as amended herein, and newly presented claims 67-70, are in condition for immediate allowance. Since nowhere in the art is this new, novel and non-obvious invention found, taught, or suggested, it is urged that this case is now clearly in condition for allowance, therefore, such action is respectfully solicited.

In the event that any additional fees may be required by the filing of this paper, an Authorization to Charge Fees to Deposit Account, **Deposit Account No. 13-1227**, is being filed concurrently with this Amendment.

Respectfully submitted,

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